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REVIEW ARTICLE

Managing multiple myeloma patients with renal failure

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Summary Renal impairment is a common and severe complication of multiple myeloma. Initial supportive treatment, especially hydration, cessation of nephrotoxic agents, avoidance of contrast for radiological studies, early treatment of infection, is often important in salvaging renal function. Bisphosphonates in patients with renal failure should be used with caution and best avoided in the initial stages, unless hypercalcemia is present. Novel criteria based on estimated Glomerular Filtration Rate (GFR) measurements are recommended for treatment in such patients and may lead to significant reversibility of renal impairment. High-dose dexamethasone therapies are highly active in myeloma patients with renal impairment. Available data support the safety and efficacy of bortezomib-based therapies in this setting, so bortezomib with dexamethasone is the recommended treatment for myeloma patients with renal impairment of any grade. A high-dose therapy with autologous stem cell transplantation can be an option for such patients; the high-dose regimen should consist of melphalan 140 mg/m^2, and the procedure should be restricted to patients younger than 60 years of age with chemosensitive disease and a good performance status.

腎臟損傷是多發性骨髓瘤的一個常見且嚴重併發症，初期的支持性療法對腎功能的拯救往往是重要的，特別是補液、腎毒性藥物的停止、顯影劑的避免、感染的盡早治療等措施。對於腎衰竭患者，除非已出現高鈣血症，否則應盡可能及早避免使用雙磷酸鹽類藥物。採用以 eGFR 為基礎的新標準，可能有助於腎臟損傷的顯著逆轉。對於出現腎臟損傷的骨髓瘤患者，高劑量 dexamethasone 是高度有效的療法。目前的數據支持 bortezomib 療法在這方面的安全性與功效，因此對於出現任何等級腎臟損傷的骨髓瘤患者，bortezomib 與 dexamethasone 是建議的合併療法。自體幹細胞移植的高劑量療法是另一選項，其中宜採用 melphalan 140 mg/m^2，治療對象應限制於 60 歲以下、對化療敏感且功能狀況良好的病人。

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Introduction

Multiple myeloma (MM) is characterized by a neoplastic proliferation of plasma cells associated, in more than 95% of cases, with the production of a single class of immunoglobulins (IgGs) known as a monoclonal protein (M protein), which can be either its subclass (e.g., IgG, IgA, or IgM) or its light chain in the serum or urine (Bence Jones protein), with IgD M protein being extremely rare.

The age-adjusted incidence rate for MM is 5.8 per 100,000 per year. It is the second most prevalent blood cancer (10%) after non-Hodgkin's lymphoma. It represents approximately 1% of all cancers and 2% of all cancer deaths. Although the peak age of onset of MM is 65—70 years, recent statistics indicate both an increasing incidence and an earlier age of onset.

It is more common in men and the Afro-Caribbean population. With the conventional treatment, median survival is 3—4 years, which may be extended to 5—7 years or longer with new forms of treatment using novel therapies.

Renal impairment is a common feature of MM; studies have shown that renal impairment is associated with inferior survival, and in particular, the presence of hypercalcemia and light chain proteinuria are the main causes of myeloma in more than 90% of cases.[1] Renal failure and infection together account for the cause of death in more than half of patients with myeloma.[2—5] At diagnosis, the serum creatinine level in 30—40% of patients with symptomatic MM is above the upper limit of normal and in approximately 20% of patients it is above 2 mg/dL. Less than 10% of patients present with severe renal failure. Renal impairment can also develop over time, and an estimated 25—50% of patients are affected during the course of their disease. Therapeutically, it is important to note that the introduction of novel chemotherapy agents such as thalidomide and bortezomib has led to improved survival in patients with MM,[6,7] and now evidence exists that this improvement also occurs in patients with renal impairment. Some studies have indicated that reversibility of renal impairment is associated with improved survival.[8—10]

Thus, a proper assessment of renal function is a mandatory part of any initial assessment when myeloma or related plasma cell disorders such as amyloidosis or IgGs deposition diseases are suspected. Conversely, plasma cell disorders are also important in the differential diagnosis of any patients presented with either acute or chronic renal failure.

Diagnostic workup

The principle of a comprehensive diagnostic workup is not only to establish the diagnosis of myeloma, but also to assess the extent of tissue damage from plasma cell infiltration and its effects on the organs affected, leading to a proper staging (Tables 1 and 2) of the disease with a view that chemotherapy, supportive therapy, and radiotherapy can be initiated.

(1) The initial workup includes a complete blood count, liver function test, bone profile (such as calcium), and proper assessment of renal function.
(2) X-rays of the skull, axial skeleton, and proximal long bones, collectively known as skeletal survey, are performed. Myeloma activity sometimes appear as "lytic lesions" (with local disappearance of normal bone due to reabsorption) and, on the skull X-ray, as "punched-out lesions" (pepper pot skull). However, such lytic lesions can be observed only in conventional plain films when more than 70% of bone trabecular is lost. Magnetic resonance imaging is more sensitive than plane X-ray in the detection of lytic lesions and may supersede skeletal survey, especially when vertebral disease is suspected. Occasionally, a computed tomographic scan is performed to measure the size of soft tissue plasmacytomas. Bone scans are typically not of any additional value in the workup of myeloma patients because there is no new bone formation and lytic lesions are not visualized well on a bone scan.
(3) Bone marrow biopsy is usually performed to estimate the percentage of bone marrow occupied by plasma cells. This percentage is used in the diagnostic criteria for myeloma. Flow cytometry can detect plasma cells that express IgGs in the cytoplasm and occasionally on the cell surface; myeloma cells are typically CD56, CD38, and CD138 positive and CD19 and CD45 negative. Cytogenetics may also be performed in myeloma for prognostic purposes for anomalies such as the deletion of chromosome 13, t (4:14), or t (14:16) 11, which confer a worse prognosis.[11]

Table 1 International Staging System.

Stage	Criteria
I	Serum β2M < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Serum β2M < 3.5 mg/L and albumin <3.5 g/dL or serum β2M 3.5—5.5 mg/L irrespective of the serum albumin
III	Serum β2M ≥ 5.5 mg/L

β2M = β2-microglobulin.

Table 2 Durie—Salmon Staging System.

Stage[a]	Criteria
I	All of the following: (1) Hb > 10 g/dL (2) Normal calcium (3) Skeletal survey: normal or single plasmacytoma or osteoporosis (4) Serum paraprotein level < 5 g/dL if IgG, <3 g/dL if IgA (5) Urinary light chain excretion <4 g/24 h
II	Fulfilling the criteria of neither Stage I nor Stage III
III	One or more of the following: 1. Hb < 8.5 g/dL 2. High calcium > 12 mg/dL 3. Skeletal survey: three or more lytic bone lesions 4. Serum paraprotein > 7 g/dL if IgG, >5 g/dL if IgA 5. Urinary light chain excretion > 12 g/24 h

Hb = hemoglobin; Ig = immunoglobulin.
[a] Stages I, II and III of the Durie—Salmon Staging System can be divided into A or B depending on serum creatinine: A, serum creatinine <2 mg/dL (<177 μmol/L) and B, serum creatinine ≥2 mg/dL (≥177 μmol/L).

(4) Other mandatory laboratory tests include quantitative measurement by protein electrophoresis and immunofixation of IgA, IgG, and IgM to establish the presence of monoclonal protein and immune paresis. It is also essential to check the level of beta 2-microglobulin, which provides prognostic information. The presence of a Bence Jones protein must be sought and, if present, a 24-hour urine quantitation for this protein is essential. The level of monoclonal protein in the serum (free light chain) or quantitation of the Bence Jones protein is important in monitoring the response to chemotherapy.

The recent introduction of a commercial immunoassay for the measurement of free light chains in the serum potentially offers an improvement in monitoring disease progression and response to treatment, particularly where the paraprotein is difficult to measure accurately by electrophoresis (e.g., in light chain myeloma or where the paraprotein level is very low). Initial research also suggests that measurement of free light chains may also be used, in conjunction with other markers, for assessing the risk of progression from monoclonal gammopathy of undetermined significance (MGUS) to MM. This serum-free light chain assay has recently been recommended by the International Myeloma Working Group for the screening, diagnosis, prognosis, and monitoring of plasma cell dyscrasias.[12]

Diagnostic criteria and classification of its subtypes

In 2003, the International Myeloma Working Group[13] agreed on the diagnostic criteria for symptomatic myeloma, asymptomatic myeloma, and MGUS.

Clinical application of this classification has widely been accepted as a key development in managing plasma cells disorders, as it helps to define at what stage the clinicians need to be considering the use of chemotherapy. Based on this classification, most clinicians have generally accepted that chemotherapy is needed in case of tissue damage related to excessive plasma cells, except in cases of more localized lytic lesions where only localized radiotherapy is indicated. So far, early chemotherapy in the absence of any tissue damage has not been shown to have any effect on the prognosis.

Clinically, myeloma has been regarded as having several subtypes; however, only symptomatic myeloma will be discussed here, as treatment is generally not needed in case of symptomatic myeloma or MGUS clinically, myeloma has been regarded as having several subtypes.

Symptomatic myeloma is defined as follows: clonal plasma cells $>$ 10% on bone marrow biopsy or (in any quantity) in biopsy from other tissues (plasmacytoma); a monoclonal protein (paraprotein) in either serum or urine (except in case of true nonsecretory myeloma).

Evidence of end-organ damage felt related to the plasma cell disorder (related organ or tissue impairment, commonly referred to by the acronym "CRAB"): hypercalcemia (corrected calcium $>$ 2.75 mmol/L); renal insufficiency attributable to myeloma; anemia (hemoglobin $<$ 10 g/dL); and bone lesions (lytic lesions or osteoporosis with compression fractures).

Note: Recurrent infections alone in a patient who has none of the CRAB features are not sufficient to make the diagnosis of myeloma. Patients who lack CRAB features but have evidence of amyloidosis should be considered to have amyloidosis and not myeloma. CRAB-like abnormalities are common with numerous diseases, and it is imperative that these abnormalities are felt to be attributable directly to the related plasma cell disorder and every attempt is made to rule out other underlying causes of anemia, renal failure, etc.

Staging

International Staging System

The International Staging System (ISS) for myeloma was published by the International Myeloma Working Group.[14]

Note that the ISS should be used only in patients who meet diagnostic criteria for myeloma. Patients with MGUS and asymptomatic myeloma who have renal dysfunction from unrelated causes such as diabetes or hypertension may have elevated β2M levels just from the renal dysfunction and cannot be considered as patients with Stage III myeloma. This is one of the main drawbacks of the ISS. Unlike staging systems used in other cancers, it does not really quantify tumor burden or extent. It is more of a prognostic index than a true staging system. For this reason, it is recommended that the ISS be used along with the Durie—Salmon Staging System (see below).

Durie—Salmon Staging System

First published in 1975,[15] the Durie—Salmon Staging System is still in use.

Pathophysiology of renal impairment in myeloma

Renal dysfunction in MM results primarily from the toxic effects of monoclonal light chains on the kidneys (light-chain-only myeloma accounts for about 15% of cases of all myeloma), in addition to other contributing factors such as dehydration, hypercalcemia, hyperuricemia, concurrent use of nephrotoxic drugs (nonsteroidal anti-inflammatory drugs, antibiotics, contrast media, etc.), and, rarely, myeloma cell infiltration or hyperviscosity due to high monoclonal protein level, especially of the IgA subclass.[16]

In more than 90% of cases of light-chain myeloma with renal impairment, renal biopsy shows the characteristic cast nephropathy with tubular atrophy and evidence of tubular interstitial fibrosis.[17]

In other cases, evidence of light-chain glomerulopathy with deposition of Igs, in either amyloid or nonamyloid form, may exist. In both glomerulopathies, the development of nonselective proteinuria is the dominant syndrome. Amyloid deposits predominate within the glomeruli and give a positive Congo red staining. In monoclonal IgGs deposition disease (MIDD), the glomerular deposits of IgGs light or heavy chains are nonfibrillar and Congo red negative.

It is crucial to remember that the pathogenesis of renal impairment is multifactorial, at least in a subset of patients with myeloma. These factors must be identified at diagnosis, as management of these factors will be essential in the reversibility of the renal impairment.

The need of a renal biopsy is not part of the standard workup for a patient with myeloma presenting with renal impairment. If the patient has proteinuria consisting mainly of light chains, a renal biopsy is not necessary. The presence of nonselective proteinuria or significant albuminuria may support the suspicion of amyloidosis or MIDD; therefore, in patients with nephrotic syndrome with or without renal failure, a renal biopsy may be necessary to search for amyloid, MIDD, or unrelated glomerulopathy such as glomerulonephritis or diabetes nephritis.

Management of myeloma patients with renal impairment

Until recently, the median survival time of MM patients with renal insufficiency was less than 1 year,[3–5,8] and patients requiring dialysis had a particularly poor prognosis. However, the prognosis for these patients has improved recently due to the availability of more effective treatments for myeloma and improvement in supportive care.

Supportive care

Adequate hydration, urine alkalization, and management of hypercalcemia are important supportive measures for the management of myeloma patients with acute renal failure, and may restore renal function in some patients.

For the treatment of hypercalcemia in myeloma patients with renal impairment, adequate hydration is necessary. Bisphosphonates have to be given according to the guidelines for estimated GFR (eGFR); intravenous bisphosphonates should be retained in patients with GFR under 30 mL/min. For zoledronic acid, dose reduction has been recommended for patients with GFR between 30 mL/min and 60 mL/min.

Drugs that may contribute to renal damage, such as nonsteroidal anti-inflammatory drugs, intravenous contrast dyes, aminoglycosides, or other antibiotics that have significant renal excretion, should be avoided. If a myeloma patient with renal failure needs intravenous contrast media for diagnostic purposes, dialysis immediately after the procedure is recommended.

Mechanical approaches

Mechanical means of treating MM patients with renal impairment include long-term dialysis, plasmapheresis, and novel dialysis filters for the removal of free light chains. Long-term dialysis is a worthwhile supportive measure for patients with MM and end-stage renal disease. If patients with dialysis-dependent renal insufficiency who die within the first 2 months of therapy (approximately 30% of the total) are excluded, then long-term dialysis in combination with conventional antimyeloma therapy can lead to a median survival time of approximately 2 years.[16] The role of plasmapheresis has been evaluated in the context of prospective clinical trials, and no clear benefit was detected.[18] The removal of free light chains with dialysis is another approach. However, the removal of such chains by a conventional dialysis membrane is restricted by their molecular weight cutoffs. A new high-cutoff hemodialysis membrane with molecular cutoffs closer to that of the native kidney (65 kDa) seemed to remove circulating light chains more efficiently and has recently been tested in the MM setting, with initial encouraging results.[19]

Chemotherapy

Bortezomib (a proteasome inhibitor)-containing chemotherapy regimen

Bortezomib is a novel antineoplastic agent and has been tested extensively in hematological malignancies, especially MM including MM in renal failure. It is cleared rapidly following intravenous administration, with peak concentrations being reached at about 30 minutes; is not excreted via kidneys; and, in animal models, has demonstrated significant antimyeloma activity.

Now, bortezomib has been accepted as safe and can be administered effectively at the full approved dose and schedule in patients with impaired renal function; in some cases, it can reverse renal failure and improve survival.[20–23] This has now replaced the traditional treatment of MM in renal failure with an infusion of vincristine/adriamycin/dexamethaxone.

In a subanalysis of the SUMMIT (Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy) and the CREST (Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma) phase 2 studies, three of 10 (30%) patients with a creatinine clearance (CRCL) of 30 mL/min and below responded to treatment, compared with a 45% overall response rate in patients with baseline CRCL of above 80 mL/min. Discontinuation rates and adverse-event profiles were similar between patients with CRCL above 80 mL/min and those with CRCL 50 mL/min and below.

The standard dose for bortezomib is 1.3 mg/m^2 intravenous bolus injections twice weekly for 2 weeks in a 3-week cycle; the total number of cycles varies between 4 and 8, depending on response and tolerance. The main side effects of this will be peripheral neuropathy and reversible thrombocytopenia. In the presence of significant neuropathy, dose reduction to 1.0 mg/m^2 or even weekly. More recently, this drug has been licensed for subcutaneous injection, which seems to have less neuropathic side effects (UK Myeloma Forum, personal communication).

The efficacy of combination therapy using bortezomib, melphalan, and prednisolone had also been demonstrated in the updated international phase III VISTA trial with longer overall survival across all subgroups defined by baseline characteristics including creatinine clearance.[24]

Immunomodulatory drug-based regimens

Thalidomide is the first immunomodulatory drug with proven activity in MM. Thalidomide pharmacokinetics are not affected by renal impairment, and thus no dose reduction is required in MM patients with renal impairment.

The standard dose of thalidomide is between 100 mg and 200 mg daily depending on the tolerance of side effects, especially marrow suppression.

In a single-center case series ($N = 20$) of patients with relapsed/refractory MM and renal impairment (defined as serum creatinine above 2 mg/dL), treatment with thalidomide alone ($n = 8$) or thalidomide plus dexamethasone ($n = 12$) resulted in 45% partial response and 30% minimal response. The median duration of response was 7 months, whereas 12/15 responding patients had improved renal function, defined as serum creatinine less than 2 mg/dL.[25]

Lenalidomide is another effective agent for the management of MM. It is excreted mainly by the kidneys, through both glomerular filtration and active tubular secretion. It is therefore not regarded as the front-line therapy for patients with myeloma presenting with renal failure, and, if used, dose reduction will be necessary to avoid toxicities. Data on its efficacy in renal failure are therefore very limited.[26]

Hematopoietic stem cell transplant

Autologous stem cell transplantation should be considered as a consolidation therapy after achieving a plateau phase with combination chemotherapy in younger patients (less than 65 years of age); the response rate can be as high as 80% with survival improved up to 18 months. The use of ASCT in patients with myeloma, renal insufficiency (serum creatinine more than 2 mg/dL), and end stage renal disease (ESRD) has also resulted in similar response rates and outcomes; however, the transplant-related mortality rate was higher, up to 13%.[27–29] In patients who have myeloma and are new to dialysis, successful use of ASCT has led to the recovery of renal function and discontinuation of dialysis in up to 24% of cases.[30,31] The role of allogeneic stem cell transplant using a human leucocyte antigen (HLA)-compatible donor is still not clear and is associated with high transplant mortality. It should be considered only in much younger patients with an HLA-compatible sibling, preferably in the context of a large clinical trial.

Conclusions

Renal impairment is a common and severe complication of MM. Initial supportive treatment, especially hydration, cessation of nephrotoxic agents, avoidance of contrast for radiological studies, and early treatment of infection, are often important in salvaging renal function. Bisphosphonates in patients with renal failure should be used with caution and best avoided in the initial stages, unless hypercalcemia is present. Novel criteria based on eGFR measurements are recommended for the treatment of such patients and may lead to significant reversibility of renal impairment. High-dose dexamethasone therapies are highly active in myeloma patients with renal impairment. Available data support the safety and efficacy of bortezomib-based therapies in this setting, so bortezomib with dexamethasone is the recommended treatment for myeloma patients with renal impairment of any grade. Lenalidomide is a feasible and effective treatment option for patients with mild to moderate renal impairment, but it should be administered at the recommended reduced dose based on renal function. Thalidomide is also an option for patients with severe renal impairment, although the data on this are less extensive. Combinations of bortezomib and immunomodulatory drugs along with high-dose dexamethasone have also shown superior antimyeloma activity to the traditional vincristine/adriamycin/dexamethaxone infusion, although no comparative studies have been performed specifically in patients with renal impairment. High-dose therapy with ASCT can be an option for such patients; the high-dose regimen should consist of melphalan 140 mg/m^2, and the procedure should be restricted to patients younger than 65 years of age with chemosensitive disease and a good performance status.

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